Spot Urine Protein:Creatinine Ratio versus 24-hour Urine Total Protein to Screen for Preeclampsia

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Objective: Our objective was to examine the accuracy of the spot urine protein:creatinine ratio using total protein in 24-hour urine specimens as the gold standard among pregnant women at risk for preeclampsia.
Methods: This was a prospective, chart review of spot and subsequent 24-hour urine tests ($\leq$7 days). Pearson correlation, receiver operating characteristics (ROC), and predictive values of the spot protein:creatinine ratio were calculated using total protein $\geq$ 300mg and recommended ratio thresholds ranging from 0.15 to 0.60.
Results: Of 302 spot tests over 18 months, 156 women had one set of eligible test results. Although strongly correlated ($r = 0.831$, $p = .0001$), the area under the ROC curve indicated fair accuracy [0.742(95%CI,0.665-0.819)]. Sensitivity ranged from 6.6%-90.8%; specificity from 38.8%-100%. Positive predictive value ranged from 58.5%-100%; negative predictive value from 53%-81.6%.
Conclusion: In our population, the spot urine protein:creatinine ratio is a poor screening tool for women at risk for preeclampsia during pregnancy.

Keywords: spot urine protein:Creatinine ratio, pre-eclampsia screening, pre-eclampsia diagnosis

Introduction

Hypertensive disease affects approximately 12-22% of all pregnancies. Gestational hypertension is defined as the development of hypertension (blood pressure greater than 140/90) after 20 weeks gestation with absence of proteinuria and return to normal blood pressures within 12 weeks postpartum. Approximately 25% of women with gestational hypertension will develop preeclampsia.[1-2]

Preeclampsia is defined as gestational hypertension with proteinuria or a total protein excretion of 300 mg or greater in a 24-hour urine specimen. Preeclampsia is further differentiated to include severe preeclampsia and HELLP syndrome. Severe preeclampsia criteria include blood pressure greater than 160/110 on 2 occasions, proteinuria 5 grams or greater in a twenty-four hour specimen, oliguria less than 500 mL in twenty four hours, cerebral or visual disturbances, pulmonary edema, epigastric pain, impaired liver function, thrombocytopenia, and fetal growth restriction.[1]

The etiology of preeclampsia is unknown, but is possibly a function of incomplete trophoblastic invasion by the placenta or possibly due to an immune system alteration.[1-2] Risk factors include first pregnancies, multifetal gestations, chronic hypertension, history of preeclampsia, pregestational diabetes, nephropathy, antiphospholipid antibody syndrome, advanced maternal age, obesity, and African American race.[1]

It is important to accurately diagnose preeclampsia, as the diagnosis affects the management of pregnancy and delivery timing. Definitive treatment is delivery of the fetus and placenta.[1-2] In pregnancy, the gold standard for quantifying proteinuria is a twenty-four hour urine collection. The disadvantages are that the process is lengthy and diagnosis can be delayed. Furthermore, it is

inconvenient for patients who must capture and store, refrigerated, all their urine for an entire day and bring it to the lab the following morning.[3] In nonpregnant patients, the spot urine protein:creatinine ratio (PCR) has largely replaced the 24-hour urine collection.[4] This involves submitting a single voided urine specimen to the lab.

Diagnostic studies among pregnant women have generally shown strong correlations between spot PCR and 24-hour urine total protein values.[5-10] Cutoffs for positive spot PCR have varied across these studies, ranging from 0.10 mm/mmol to 0.6mm/mmol, resulting in widely varied biometrics (i.e., sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratios, etc). The International Society for the Study of Hypertension in Pregnancy (ISSHP) standardized the spot PCR cutoff at >0.3 mm/mmol in 2001[11] and a systematic review and meta-analysis of articles from 1997 through 2008 confirmed this cutoff for adequate sensitivity and specificity and described use of the spot PCR as "promising."[5]

The objective of this study was to examine the use of spot PCR as a screening tool for preeclampsia in our pregnant patients. Specifically, we sought to determine the correlation of spot PCR with total protein from 24-hour urine specimens and the sensitivity, specificity, and positive predictive value of spot PCR in our practice.

Methods

We conducted a prospective chart review of all patients undergoing spot PCR on the day a 24-hour urine test was ordered. Subjects were all comers to MAHEC OB clinic being evaluated for preeclampsia with a 24-hour urine or patients with chronic hypertension establishing a baseline 24-hour urine total protein. All patients participating in this study gave consent for care. Patients were given the supplies for the 24-hour urine testing after providing the spot urine sample; patients were not billed for the spot PCR.

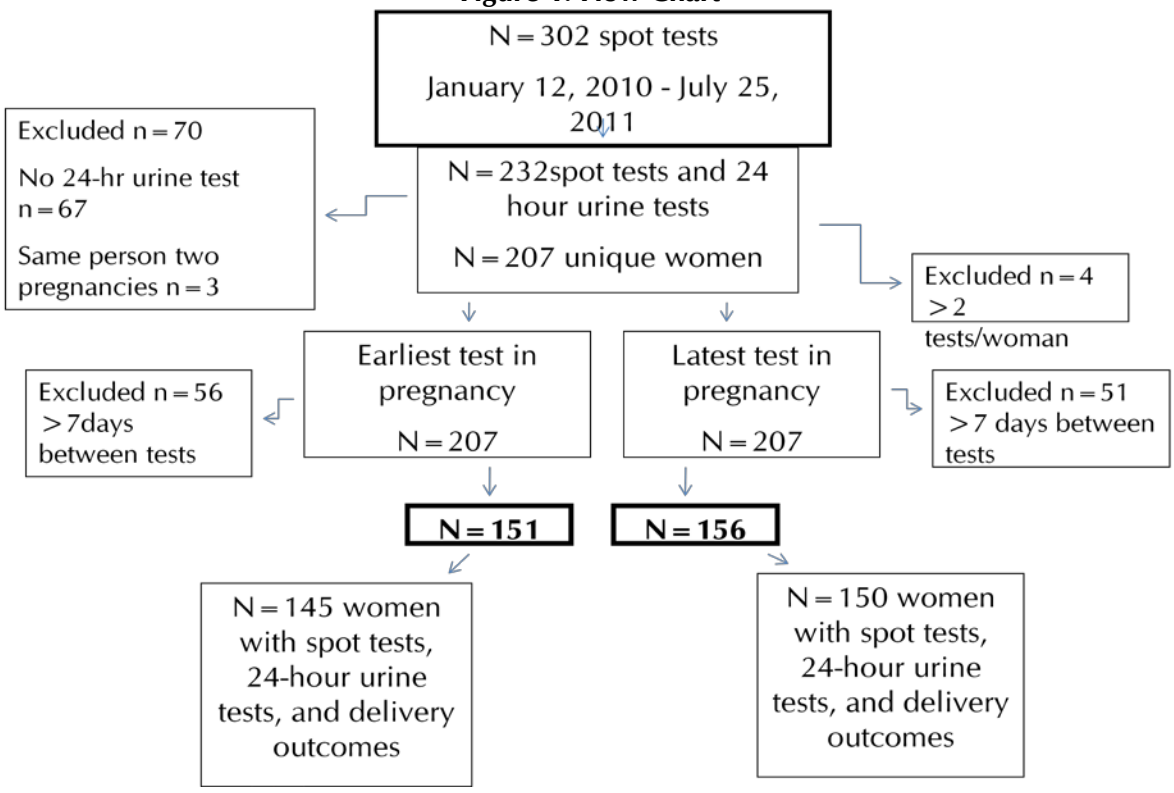
Copies of the lab reports were provided by the lab techs to the research team. We extracted additional data from medical records including: age, race, parity, weight, blood pressure, other medical comorbidities, and delivery outcomes.

We used the Pearson correlation to examine the relationship between spot PCR and the total protein on the 24-hr urine test. Sensitivity, specificity, positive predictive value, and negative predictive value were then calculated using spot ratio cutoffs common to other studies. Area under the ROC curve was also calculated.

Results

A total of 302 spot tests were collected between January 12, 2010 and July 25, 2011. Sixty-seven 24-hour urine specimens were not returned. Three samples involved the same person in two pregnancies, and these were excluded. Of 232 remaining tests, 207 belonged to unique women. For women with multiple tests in pregnancy, the test at the latest gestational age was utilized. Fifty-one tests were excluded because there was greater than seven days between spot PCR collection and 24-hour urine collection. Patient characteristics were examined for N = 156. Delivery outcome data was available for 150 of 156 (see Figure 1).

Figure 1. Flow Chart

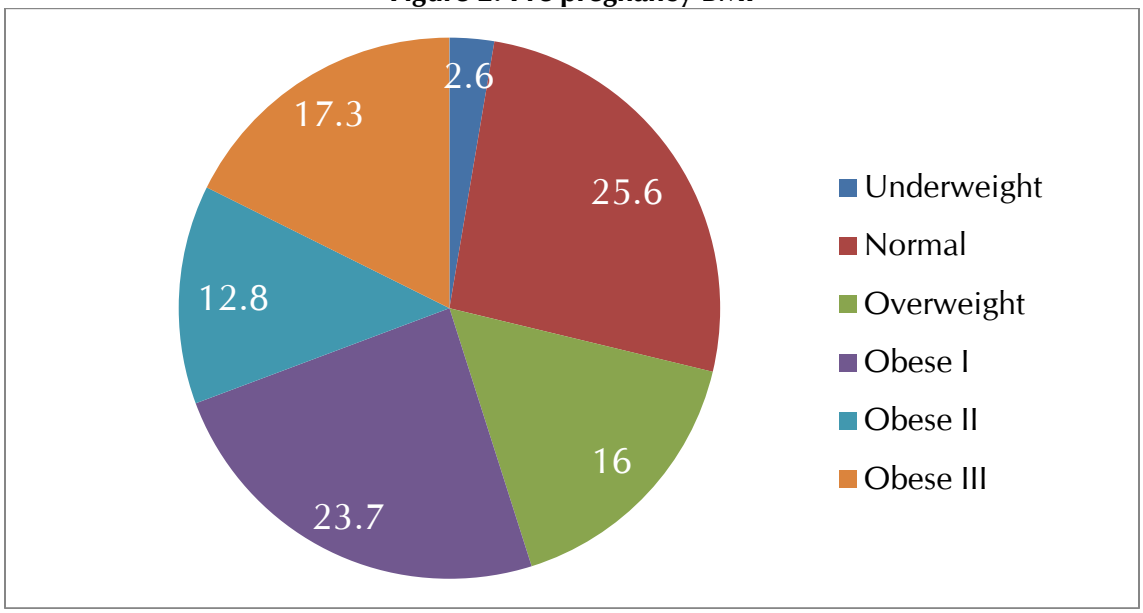


Patients' ages ranged from 16 to 44 years (Median age = 27.6). The majority of patients were white, multiparous, and obese (see Table 1 and Figure 2). Only 2 patients (1.3%) had a multiple gestation. Forty-four women had pre-existing hypertensive disease (28.3%), and 22 (14.1%) had a history of preeclampsia. Nearly 1 in 5 women had diabetes, and nearly 1 in 5 women smoked during this pregnancy.

Table 1. Patient Characteristics

TOTAL PATIENTS N = 156		N(%)
Age Median years (minimum-maximum)		27.6 (16.3-44.6)
Race/Ethnicity	Black	14 (9)
	White	114 (73)
	Hispanic	23 (14.7)
	Other	5 (3.2)
Multiparous		104 (66.7)
Multiple Gestations		2 (1.3)
Smoked during Pregnancy		36 (23.1)
Diabetes	Pre-gestational	30 (19.2)
	Gestational	11 (7.1)
Hypertension	Chronic	37 (23.7)
	Pregnancy Associated	7 (4.5)
History of Preeclampsia		22 (14.1)

Figure 2. Pre-pregnancy BMI



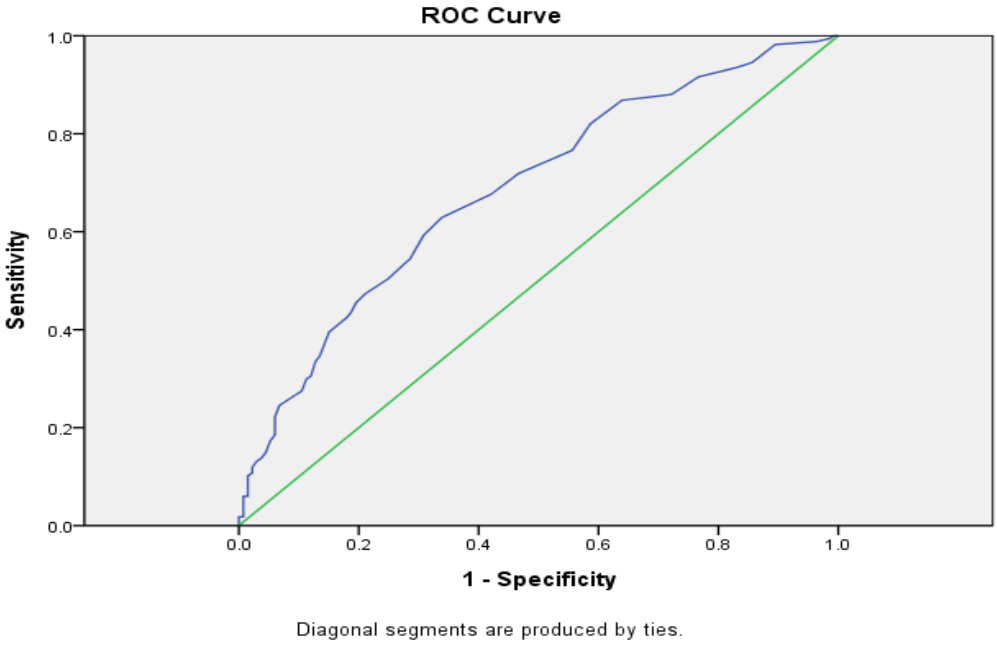
Approximately 1 in 3 spot PCRs were performed on urine from women who were less than 20 weeks gestation (see Table 2). On the day of the spot PCR, the majority had elevated blood pressures (>140 systolic and/or >90 diastolic). At the time patients returned 24-hour urine tests, nurses checked blood pressures of 108 women; 18.5% of these women had elevated blood pressures. Median time between spot PCR and 24-hour total protein was 3 days (range: 1-7 days).

Table 2. Patient Characteristics at Spot Urine PCR and 24-hour Urine Total Protein

TOTAL PATIENTS N=156	N(%)
Gestational Age	
<20 weeks	50 (32.1)
≥20 weeks	106 (67.9)
Elevated Blood Pressure	
At Spot Test	61 (59.6)
Unknown	2 (1.3)
At 24 hr. urine test	20 (12.8)
Unknown	48 (30.8)
Days Between spot & 24 hr. urine tests	
Median (minimum-maximum)	3 (1-7)

The correlation between PCR and 24-hour urine total protein was strong and significant (R=0.831; p=0.0001). Accuracy, however was fair with the Area under ROC=0.742 (95% CI, 0.665-0.819; see Figure 3).

Figure 3. PCR Biometrics



When we used a cutoff ≥0.30 to compare to a value of 300 mg total protein, accuracy was 93/156 or 59.6%. This would include 25 true positive and 68 true negative; however, 51 women with proteinuria ≥300 mg would have false negative spot PCR. Twelve (23.5%) of these women had elevated blood pressure at the time their spot PCR was collected. Twelve women had false positive spot PCR resulting in unnecessary 24-hour urine tests. None of the possible cutoffs yielded acceptable biometrics (see Table 3). Spot PCR did not fare well enough to use it as a pre-screen to decide who should complete a 24-hour urine test.

Table 3. Biometric Properties of Spot Urine PCR with 24-hour Total Protein as the Gold Standard

CUTOFF	SENSITIVITY	SPECIFICITY	PPV	NPV
0.15	90.8	38.8	58.5	81.6
0.19	76.3	65.0	67.4	74.3
0.21	61.8	71.3	67.1	66.3
0.28	35.5	83.8	67.5	57.8
0.3	32.9	85.0	67.6	57.1
0.6	6.6	100.0	100.0	53.0

Birth outcomes were available for 150/156 (96.2%) of the patients. Preeclampsia was diagnosed in 53 women (35.3%; mild, severe, or superimposed). Thirty-one mothers (20.7%) delivered preterm; the majority for medical indications (see Table 4). Fifty-nine women (39.3%) delivered via cesarean section; 27 (18%) were primary cesarean deliveries.

Table 4. Birth Outcomes

TOTAL PATIENTS N=150		N (%)
Preeclampsia Diagnosis	Mild	26 (17.3)
	Severe	12 (8)
	Superimposed on cHTN	15 (10)
Preterm Delivery (<37 wks)		31 (20.7)
	Spontaneous	6 (19.4)
	Medically Indicated: Pre-eclampsia	17 (54.8)
	Medically Indicated: Other diagnosis	8 (25.8)
Induction of Labor		74 (49.3)
Route of Delivery	Spontaneous vaginal	86 (57.3)
	VBAC	3 (2)
	Operative vaginal	2 (1.4)
	Primary cesarean	27 (18)
	Repeat cesarean	32 (21.3)

Conclusions

Despite a strong relationship between spot PCR ratio and 24-hour total protein consistent with the literature[5-11], accuracy of testing was only fair. Using the ISSHP cutoff of >0.30[11] still resulted in less than acceptable accuracy. We included all comers needing either a baseline or diagnostic total protein values in our study to reflect the typical clinical use of the 24-hour urine testing we hoped to limit by adding an acceptable screening tool – the PCR. For us, screening for proteinuria in pregnancy with only spot urine PCR remains suboptimal.

Our results may be limited by our inclusion of baseline urine protein testing; our sample size was too small, however, to conduct a meaningful analysis on these subsets of tests. Further, we did not exclude women with symptomatic or asymptomatic bacteria. The inclusion of these urine samples in our analyses may have contributed to the limited accuracy of the PCR inconsistent with other studies using the ISHHP cutoff.[6-9] Other limitations of our study include the small sample size that was limited by the number of women who did not complete 24-hour urine study. The patient characteristics in this study illustrate our regions' high-risk obstetric population with hypertension: a large proportion have medical comorbidities including overweight, obesity, diabetes, and almost 1 in 4 smoke tobacco during pregnancy. The need for screening and diagnosing preeclampsia is unlikely to decline unless both individual and community-wide behavioral changes become priorities.

With 22% of patients not completing recommended testing and a considerable delay between ordering and completing the testing for another 27.1%, the need for a more convenient test and/or screening process is evident. Further study into the use of spot urine PCR in our pregnant patients is warranted in an effort to provide clinicians with quicker information that should improve the quality of care we provide and our patients' birth outcomes.

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